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USE OF SELECTED OXIDIZING AGENTS FOR THE ANALYSIS OF PHENOTHIAZINE DERIVATIVES

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Use of Selected Oxidizing Agents for the Analysis of Phenothiazine Derivatives" submitted by Richard Donald Krause in partial fulfilment of the requirements for the degree of Master of Science.

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ABSTRACT

Attempts were made to develop a quantitative assay procedure for phenothiazine derivatives involving titration with copper(II) in acetonitrile in which the endpoint was determined amperometrically or photometrically. A possible explanation of the unfavorable results obtained is postulated.

A method was developed in which phenothiazine derivatives were titrated to a colorless endpoint with ceric sulfate. Quantitative recoveries were obtained only for chlorpromazine, acetylpromazine, trifluoperazine and triflupromazine. The method was also applied to pharmaceutical dosage forms of these drugs. A possible explanation is advanced for the unfavorable results obtained for other phenothiazines investigated.

The endpoint in the titration of phenothiazine derivatives with ceric sulfate was also detected photometrically by following the absorbance of the sulfoxide in the ultraviolet region. This method was found to be applicable only to phenothiazine derivatives which were substituted with a thioalkyl group in the 2-position.

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(pyrathiazine base); Sandoz Pharmaceuticals (thiethylperazine dimaleate, thioridazine base, thioridazine HCl); Smith, Kline and French Inter-American Corporation (trifluoperazine base, trifluoperazine 2HCl, Stelazine ® 10 mg. Tablets, Stelazine ® 1 mg./ml. Injection); Paul Maney Laboratories Canada Ltd. (Chlorpromanyl ® 10 mg. Tablets, Chlorpromanyl ® 25 mg./ml. Injection).

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INTRODUCTION

Since the synthesis of chlorpromazine in 1950 by Charpentier, Gaillot and Gaudechon (1) in the Rhone-Poulenc-Speciá laboratories in France, a great number of phenothiazine derivatives have been synthesized and tested pharmacologically.

The principal pharmacological effect of chlorpromazine and other phenothiazine derivatives is their tranquilizing action. Agitated psychotic and psychoneurotic patients may be calmed and made more receptive to psychotherapy by the administration of these drugs. This utilization of the tranquilizers has done much to decrease the patient load on mental hospitals. In addition to their behavioral effects, these drugs are potent antiemetics and also have antihistaminic properties (2).

Volume 9 of Advances in Heterocyclic Chemistry (3) contains a chapter by Bodea and Silborg which reviews recent advances in the chemistry of phenothiazines. Blazek, Spinkova and Steijkal (4) and Blazek (5) have published reviews on the analysis of phenothiazine derivatives. Both reviews contain a section of oxidimetric methods.

In 1940, Michaelis, Schubert and Granick (6) showed by potentiometric titration that the oxidation of phenothiazine and several of its derivatives in acidic media proceeds univalently through two successive and distinct steps. Figure 1 shows the sequence of events in the oxidation of an N-substituted phenothiazine derivative (I).

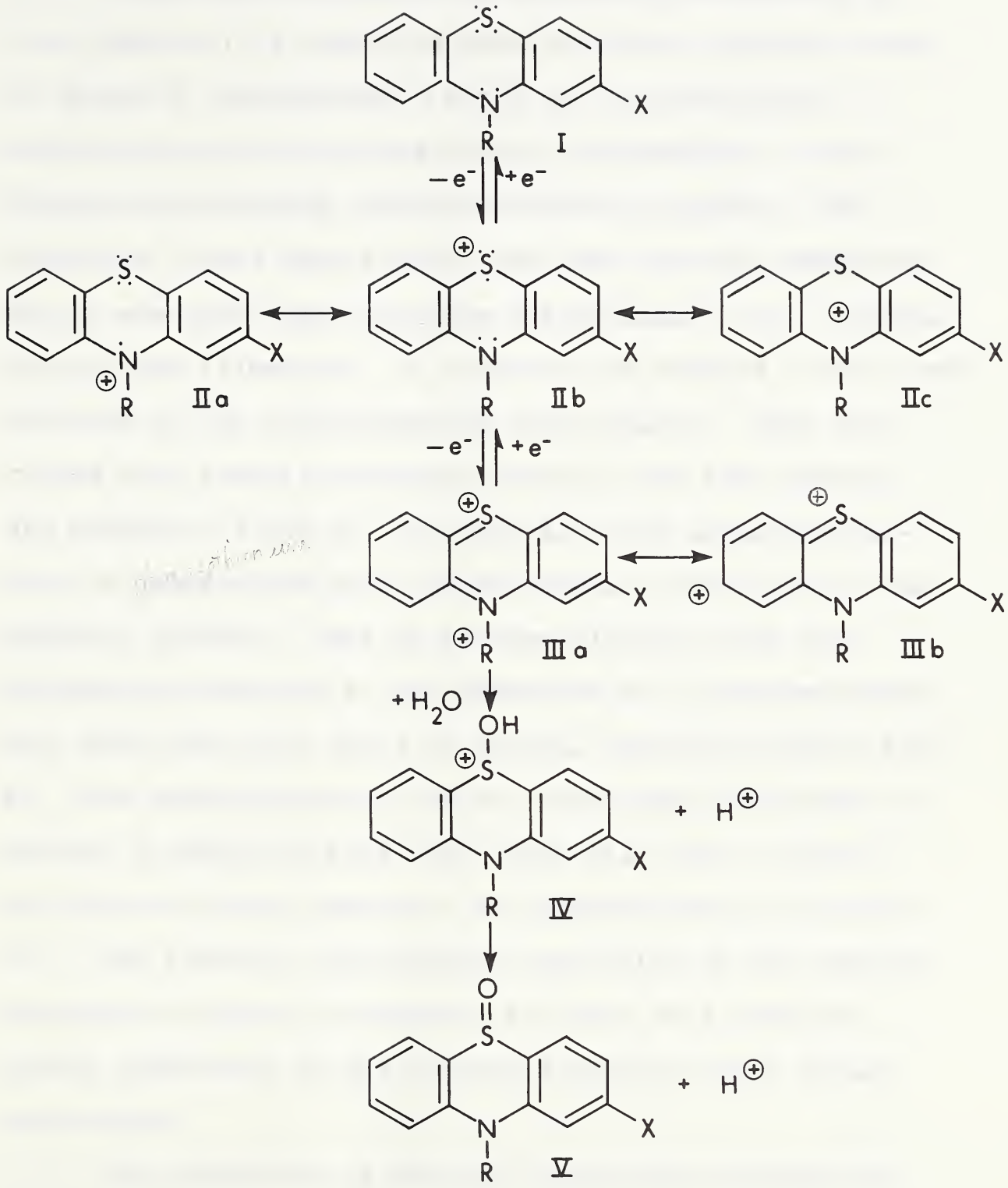


FIGURE 1 - THE SEQUENCE OF EVENTS IN THE OXIDATION OF AN N-SUBSTITUTED PHENOTHIAZINE DERIVATIVE

The highly-colored, odd electron intermediate or free radical (II) resulting from the first oxidation step is called a "semiquinone", based on its structural similarities with the free radical intermediate in the hydroquinone-quinone oxidation-reduction system. The existence of the free radical has been directly demonstrated by electron spin resonance spectroscopy (7,8). Merkle, Discher and Felmeister (9) isolated and studied a solid perchlorate of the chlorpromazine free radical. They concluded that several resonance forms of the free radical are possible (IIa,b,c). In form IIc, the unshared electron is delocalized into the molecular pi orbitals of the aromatic nucleus. Loss of another electron from this intermediate results in the formation of a phenazathionium ion, which can also exist in several resonance forms (IIIa, b). The phenazathionium ion can then react with water to produce a sulfonium base (IV) which will lose a proton to yield the final product - the phenothiazine sulfoxide (V). The internal electrostatic repulsion of the phenazathionium ion might be expected to force this reaction almost completely in the forward direction under normal conditions.

The formation of colored semiquinone products by the action of a variety of oxidizing agents has been used for the detection and assay of phenothiazine derivatives. For example, Fossoul (10) oxidized promethazine with

ammonium persulfate and measured spectrophotometrically at 520 mμ the red color produced. The color was found to be stable for more than one hour. Dubost and Pascal (11) noting that chlorpromazine gave a red color when treated with sulfuric acid, developed a method which could be used to estimate the amount of chlorpromazine which was extracted with ether from the blood and urine of rabbits.

Dusinsky (12) found that the oxidation of diethazine with solutions of permanganate, dichromate, iodine, nitrite and bromate did not yield quantitative results. Quantitation was possible when oxidizing with bromate in the presence of potassium bromide; with ceric sulfate in 1 to 2N sulfuric acid; and with chloramine-T in the presence of potassium bromide. However, the last mentioned reaction was not fast enough to be used for analytical purposes.

Dusinsky (13) and Dusinsky and Liskova (14) determined the optimum conditions for the oxidimetric titration of chlorpromazine, prochlorperazine, diethazine and promethazine. When ceric sulfate was used as the oxidizing agent, they found that the optimum concentration of sulfuric acid to employ as solvent was 0.1 to 1N for chlorpromazine and prochlorperazine, 1 to 1.5N for diethazine and 1.2 to 1.4N for promethazine. In the bromimetric determination, they found that the optimum concentration of hydrochloric acid in the solvent for all four compounds

was 2 to 3N. During the titration, the red color of the free radical increased in intensity as titrant was added and reached a maximum when one equivalent of oxidant had been added. As the titration progressed past this point, the intensity of the color decreased, with complete decolorization occurring after two electrons had been removed. The endpoint for chlorpromazine, prochlorperazine and diethazine was determined visually by the decolorization technique. An electrochemical method, either dead-stop or potentiometric, was used to determine the endpoint for promethazine.

Berka, Prochazkova and Zyka (15) attempted to discover if lead tetraacetate was analogous in oxidative activity to the reagents in the cerimetric and bromimetric titration procedures of Dusinsky and Liskova. They found that the endpoint could not be determined visually by complete decolorization of the solution, and that it had to be determined potentiometrically. The results they obtained with lead tetraacetate for chlorpromazine and promethazine were similar to those obtained cerimetrically. However, results obtained for diethazine were high.

A group of Czechoslovakian workers (16,17,18,19,20) titrated various phenothiazine derivatives with ceric sulfate and detected the endpoint amperometrically by means of two platinum electrodes. Optimum conditions,

including potential difference between the two electrodes, concentration of sulfuric acid in the solvent, rate of addition of titrant, amount of drug titrated and total volume of solution were presented for promethazine, levomepromazine, chlorpromazine and butaperazine. Procedures and results were also given for various pharmaceutical dosage forms. The amperometric titration curve showed that the current intensity increased to a maximum after the addition of half of the theoretical equivalent of titrant, or after one electron had been removed from the drug. The current then decreased to a constant value at the endpoint. A parallel intensification of a red color and its gradual disappearance was also observed.

Blazek (21) studied the possibilities of the oxidimetric determination of acetylpromazine, dichlorpromazine, chlorpromazine and triflupromazine. He found that potassium bromate was suitable only for the determination of chlorpromazine; in other instances the reaction proceeded very slowly and the results were unreliable. In studying the effect of the acidity, concentration of the substance and temperature, it was found that the best results were obtained at room temperature by titration with ceric sulfate in 0.1 to 1N sulfuric acid, using 10 to 100 mg. of the substance. At temperatures above 20°, no reliable results could be obtained.

Muinier, Viossat, Letterrier and Douzou (22) found that antimony pentachloride reacted with several phenothiazine derivatives by a mechanism involving a free radical to give colored products. The method was used for the qualitative and quantitative spectrophotometric determination of phenothiazine, propericiazine, thioproperazine and thioridazine in dichloroethane, and was applied to the analysis of these phenothiazines in biological media, especially urine.

Merkle and Discher (23) found that controlled potential electrolysis was suitable for the coulometric determination of several pharmaceutically important N-substituted phenothiazines. The compounds could be quantitatively oxidized to the free radical in 12N sulfuric acid. After this oxidation all the solutions had an intense color characteristic of the particular compound oxidized: chlorpromazine, red; promethazine, red; promazine, orange-brown; triflupromazine, orange; trifluoperazine, orange; prochlorperazine, red; thioridazine, blue. The acid-stabilized free radical was oxidized to a colorless sulfoxide by increasing the applied potential. Oxidation of the compounds directly to the sulfoxide stage was accomplished by using acid concentrations lower than those necessary to stabilize the free radical intermediate.

Agarwal and Blake (24) titrated various phenothiazines and some dosage forms with ceric sulfate. The

endpoint was determined photometrically by following the reaction at 420 mμ, which is the wavelength of maximum absorbance of ceric sulfate. They reported quantitative recoveries for trimeprazine, chlorpromazine, fluphenazine, methdilazine, thiopropazate, prochlorperazine, perphenazine, acetophenazine, trifluoperazine and mepazine. Good agreement was also obtained between the label claim value and recovered amount for thiopropazate tablets and chlorpromazine syrup.

Semaka (25) attempted to develop a quantitative assay procedure for phenothiazine derivatives based on the color produced in a perchloric acid-nitromethane system. Linear relationships between concentration and absorbance were obtained for the majority of the phenothiazines investigated. A satisfactory procedure was developed for three phenothiazines in tablet dosage form, but for the majority of the tablet preparations and for all the syrups, suppositories, suspensions and ampoules investigated, no quantitative procedure was achieved.

The 1963 edition of the British Pharmacopoeia (26) included an oxidimetric assay procedure for chlorpromazine tablets using ceric sulfate as titrant and dilute sulfuric acid as solvent. The endpoint was determined visually using phenanthroline-ferrous complex solution as indicator. This method is not included in the 1968 edition of the British Pharmacopoeia.

STATEMENT OF THE PROBLEM

One of the principal reactions of phenothiazine derivatives is their ability to give rise to different oxidation products by successive electron loss. A number of references have appeared in the literature describing attempts by Czechoslovakian workers to quantitatively analyze several pharmaceutically important phenothiazine derivatives and their dosage forms by titration with standardized solutions of various oxidizing agents, notably ceric sulfate. One of the purposes of this investigation was to develop a simple titrimetric assay procedure for phenothiazine derivatives, using ceric sulfate as titrant, and to apply it to various phenothiazine dosage forms currently on the Canadian market.

Nonaqueous solvent systems have not yet been extensively utilized in oxidation-reduction reactions. In view of a report that copper(II) acts as a strong oxidizing agent in acetonitrile, it was proposed to study the application of this system to the quantitative analysis of phenothiazine derivatives.

EXPERIMENTAL

APPARATUS

A. GENERAL

Low-actinic volumetric flasks, magnetic stirrers, Kimax 5 ml. microburette equipped with a platinum tip, conventional laboratory glassware.

B. AMPEROMETRIC TITRATIONS

A Sargent Model XV Polarograph was used to adjust the potential difference between the electrodes and to measure the current passing between them during titration. The indicating electrode was a Sargent S-30421 platinum electrode rotated at 600 r.p.m. by a Hagen synchronous motor (Hagen Manufacturing Co., Inc., Baraboo, Wisconsin). The reference electrode was a Fisher saturated calomel electrode (Cat. No. 13-639-62) fitted with a sintered glass collar.

The titration vessel itself was a glass H-cell, the connecting arm of which was fitted with a sintered glass disc and filled with an agar plug saturated with potassium chloride. The reference electrode was placed in the smaller compartment of the H-cell, which was then filled with a saturated solution of potassium chloride and sealed. The larger compartment of the H-cell was made of blue glass to reduce photodegradation of the phenothiazines. It was fitted at the bottom with a capillary tube through which nitrogen could be bubbled before titration

to remove dissolved oxygen, and a teflon stopcock to drain the solutions after titration. The capacity of this compartment was about 150 ml.

C. PHOTOMETRIC TITRATIONS

A Beckman Model DB spectrophotometer equipped with a Beckman No. 96160 flow cell assembly was used. The titration vessel, which was originally described by Rehm, Bodin, Connors and Higuchi (28), was a 50 ml. Erlenmeyer flask equipped with an outlet tube sealed tangentially at the lowest part of the side and an inlet tube which entered the bottom of the flask at its center. These two tubes are bent in order to be parallel (Figure 2). The titration flask and absorption cell were connected with short lengths of 3 mm. rubber tubing. A stirring bar was placed in the flask which was supported over a magnetic stirrer. The solution was circulated through the tubing to the cell and back to the flask by the action of the stirring bar.

REAGENTS

Glacial acetic acid A.C.S.; 0.1N perchloric acid in glacial acetic acid (standardized against potassium acid phthalate primary standard); 6% mercuric acetate in glacial acetic acid; 0.5% crystal violet in glacial acetic acid; 0.01M disodium ethylenediamine tetraacetic-

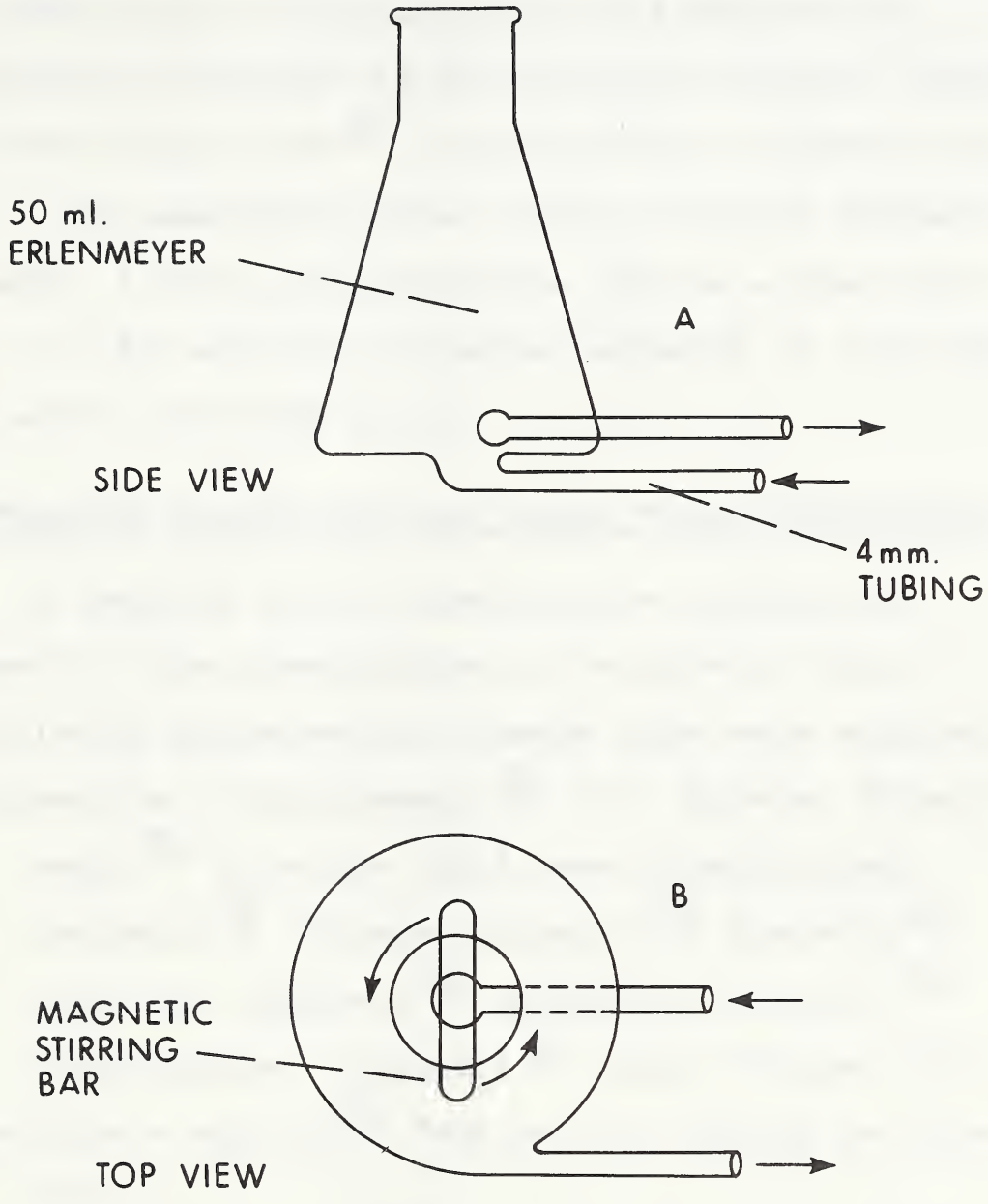


FIGURE 2 - PHOTOMETRIC TITRATION VESSEL

acid; copper metal (BDH Analar); 0.1% α-pyridyl-β-azonaphthol in 95% ethanol; acetonitrile A.C.S.; 0.001M and 0.005M copper (II) perchlorate in acetonitrile; 0.1N sodium perchlorate in acetonitrile; nitrogen (grade G); 0.02% Triton X-100® in acetonitrile; sulfuric acid A.C.S.; ceric ammonium nitrate; arsenic trioxide (primary standard); 0.025M o-phenanthroline ferrous sulfate complex; 1 in 400 solution of osmium tetroxide in 0.1N sulfuric acid; chloroform A.C.S.

PHENOTHIAZINE DERIVATIVES AND DOSAGE FORMS INVESTIGATED

A complete list of phenothiazine derivatives utilized in this investigation is included in Table I. The following pharmaceutical dosage forms were analyzed:

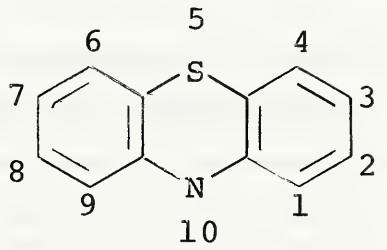
Chlorpromazine - Chlorpromanyl® "10" Tablets, Chlorpromanyl® Injection (Paul Maney Laboratories); Largactil® Tablets, Largactil® Spansule® Capsules, Largactil® Injection, Largactil® Suppositories, Largactil® Liquid (Poulenc Ltd.)

Fluphenazine - Moditen® Tablets (E.R. Squibb and Sons Ltd.)

Triflupromazine - Vesprin® Injection (E.R. Squibb and Sons Ltd.)

Trifluoperazine - Stelazine® Tablets, Stelazine® Injection (Smith, Kline and French)

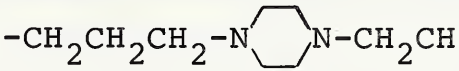
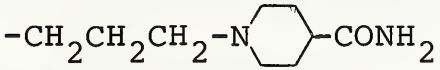
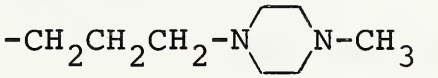
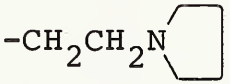
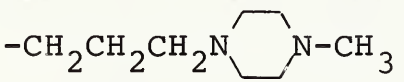
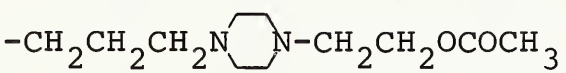
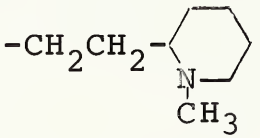
TABLE I. PHENOTHIAZINE DERIVATIVES INVESTIGATED



GENERIC NAME OF DRUG	2-POSITION SUBSTITUENT	10-POSITION SUBSTITUENT	TRADE NAME	MANU-FACTURER
ACETYLPROMAZINE	$-COCH_3$	$-CH_2CH_2CH_2N(CH_3)_2$	ATRAVET	AYERST
AMINOPROMAZINE	-H	$-CH_2-CH(N(CH_3)_2)-CH_2N(CH_3)_2$	LISPAMOL	POULENC
CHLORPROMAZINE	-Cl	$-CH_2CH_2CH_2N(CH_3)_2$	CHLORPROMANYL LARGACTIL	PAUL MANEY POULENC
FLUPHENAZINE	$-CF_3$	$-CH_2CH_2CH_2-N$ (piperazine) $N-CH_2CH_2OH$	MODITEN	SQUIBB
LEVOMEPROMAZINE	$-OCH_3$	$-CH_2CH(CH_3)CH_2N(CH_3)_2$	NOZINAN	POULENC
MEPAZINE	-H	$-CH_2-$ (piperidine) $-N-CH_3$	PACATAL	WARNER-CHILCOTT
METHDILAZINE	-H	$-CH_2-$ (pyrrolidine) $-N-CH_3$	TACARYL	MEAD-JOHNSON

...CONTINUED

TABLE I (CONTINUED) PHENOTHIAZINE DERIVATIVES INVESTIGATED

GENERIC NAME OF DRUG	2-POSITION SUBSTITUENT	10-POSITION SUBSTITUENT	TRADE NAME	MANU-FACTURER
PERPHENAZINE	-Cl		TRILAFON	SCHERING
PIPAMAZINE	-Cl		MORNIDINE	SEARLE
PROCHLORPERAZINE	-Cl		STEMETIL	POULENC
PROMAZINE	-H	$-CH_2CH_2CH_2N(CH_3)_2$	SPARINE	WYETH
PROMETHAZINE	-H	$-CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HN(CH_3)_2$	PHENERGAN	POULENC
PYRATHIAZINE	-H		PYRROLAZOTE	UPJOHN
THIETHYLPERAZINE	$-SCH_2CH_3$		TORECAN	SANDOZ
THIOPROPAZATE	-Cl		DARTAL	SEARLE
THIORIDAZINE	$-SCH_3$		MELLARIL	SANDOZ

...CONTINUED

TABLE I. (CONTINUED) PHENOTHIAZINE DERIVATIVES INVESTIGATED

GENERIC NAME OF DRUG	2-POSITION SUBSTITUENT	10-POSITION SUBSTITUENT	TRADE NAME	MANU-FACTURER
TRIFLUOPERAZINE	$-CF_3$	$-CH_2CH_2CH_2N\langle\rangle NCH_3$	STELAZINE	SMITH, KLINE & FRENCH
TRIFLUPROMAZINE	$-CF_3$	$-CH_2CH_2CH_2N(CH_3)_2$	VESPRIN	SQUIBB
TRIMEPRAZINE	-H	$-CH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2N(CH_3)_2$	PANECTYL	POULENC

PROCEDURES

A. DETERMINATION OF PURITY OF THE PHENOTHIAZINE DERIVATIVES

A quantity of the pure drug approximately equal to 0.1 meq. (25 to 40 mg.) was accurately weighed into a 100 ml. beaker and dissolved in 30 ml. of glacial acetic acid. The titrant was 0.1N acetous perchloric acid. Two drops of 0.5% crystal violet indicator in glacial acetic acid were added and the solution was titrated to a blue endpoint with the aid of a magnetic stirrer and a titration lamp. A blank titration was performed on the solvent and subtracted. Two ml. of 6% mercuric acetate in glacial acetic acid was added if the phenothiazine was a halide salt.

B. STANDARDIZATION OF COPPER(II) PERCHLORATE TITRANT IN ACETONITRILE

A 0.01M solution of the disodium salt of ethylenediaminetetraacetic acid (EDTA) in water was standardized against pure copper metal (BDH Analar) by the following method: about 100 mg. of copper was accurately weighed, dissolved in 2 ml. of concentrated nitric acid and diluted to 100 ml. A 5 ml. aliquot of this solution was transferred to the titration vessel, 5 ml. of a pH 4.5 ammonia-ammonium acetate buffer and 2 drops of 0.1% α-pyridyl-β-azonaphthol (PAN) in 95% ethanol added, the

solution diluted to about 90 ml. with distilled water, heated to 80°C and titrated with the EDTA solution. At the endpoint the color changed from violet to yellow.

The standardized EDTA solution was then used to standardize 0.005M and 0.001M solutions of copper(II) perchlorate in acetonitrile. A 5 ml. aliquot of the acetonitrile solution was treated in the same manner as above.

C. AMPEROMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES

A stock solution was prepared containing about 40 mg. of the phenothiazine free base in 50 ml. of acetonitrile. A 5 ml. aliquot of this solution along with 50 ml. of 0.1N sodium perchlorate and 1 ml. of 0.02% Triton X-100 ® in acetonitrile was transferred to the titration vessel. A stream of nitrogen was bubbled through the solution for ten minutes to remove dissolved oxygen. This solution was used to record a polarogram of the phenothiazine derivative. A potential more negative than the half wave potential, on the plateau region of the curve, was chosen for the amperometric titration. The titrant, 0.001M copper(II) perchlorate in acetonitrile, was added in 1 ml. increments and readings were taken 30 seconds after the addition of each increment. The amount of current flowing after each addition was plotted against the volume of titrant added and the endpoint taken at the change of slope of the graph.

D. PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH COPPER(II)

A stock solution was prepared containing about 50 mg. of the phenothiazine free base in 25 ml. of acetonitrile. A 2 ml. aliquot of this solution was transferred to the titration vessel of the photometric titration apparatus and diluted to 30 ml. with additional acetonitrile. One ml. of titrant, 0.005M copper(II) perchlorate in acetonitrile, was added to the solution which was then scanned in the visible region to determine the wavelength of maximum absorbance. This wavelength was used for the photometric titration. The titration vessel and flow-through cell were then drained and rinsed with acetonitrile, another aliquot of drug added and diluted. The titrant was added from a 5 ml. microburette in 0.4 ml. increments and the absorbance read thirty seconds after the addition of each increment. The absorbance of the solution after each addition was plotted against the volume of titrant added and the endpoint taken at the change of slope of the graph.

E. PREPARATION AND STANDARDIZATION OF 0.05M CERIC SULFATE

Fifteen ml. of sulfuric acid was added to 29.5 gm. of ceric ammonium nitrate in a beaker. Water was added in 20 ml. portions until solution was complete, then the beaker was covered and allowed to stand overnight. The solution was filtered through a fine-porosity

sintered glass crucible, diluted to 1000 ml. and mixed. About 200 mg. of arsenic trioxide, previously dried at 100°C for one hour, was accurately weighed and transferred to a 500 ml. Erlenmeyer flask. The inner walls of the flask were washed down with 25 ml. of sodium hydroxide solution (2 in 25), the sample dissolved by swirling, and 100 ml. of distilled water and 10 ml. of dilute sulfuric acid (1 in 3) added. After the addition of two drops each of 0.025M o-phenanthroline ferrous sulfate complex and a 1 in 400 solution of osmium tetroxide in 0.1N sulfuric acid, the solution was titrated with the ceric sulfate solution until the pink color changed to a pale blue.

F. PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

A stock solution was prepared containing about 25 mg. of the drug in 100 ml. of 2N sulfuric acid. A 1 ml. aliquot of this solution was transferred to the titration vessel of the photometric titration apparatus and diluted to 25 ml. with additional 2N sulfuric acid. The flow cell was put in place and the spectrophotometer was set at the appropriate wavelength in the ultraviolet region which was 275 mμ if the substituent in the 2-position of the phenothiazine derivative was $-SCH_3$ or $-SCH_2CH_3$ or 270 mμ if this substituent was -H, -Cl, $-OCH_3$, $-CF_3$ or $-COCH_3$. The titrant, 0.005M ceric sulfate, was added in 0.05 ml. increments

from a 5 ml. microburette and the absorbance read thirty seconds after the addition of each increment. The absorbance of the solution after each addition was plotted against the volume of titrant added and the endpoint taken at the change of slope of the graph.

G. VISUAL TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

About 10 mg. of the phenothiazine was accurately weighed into a 10 ml. beaker and dissolved in 5 ml. of dilute sulfuric acid. The titrant was 0.05M ceric sulfate. The solution was titrated with the aid of a magnetic stirrer and a titration lamp. The endpoint was taken at complete decolorization of the solution.

H. VISUAL TITRATION OF PHARMACEUTICAL DOSAGE FORMS WITH CERIC SULFATE

1. Tablets

Twenty tablets were weighed and powdered. A sample of powder approximately equivalent to 10 mg. of the active ingredient was accurately weighed into a 10 ml. beaker. Five ml. of 2N sulfuric acid was added and the suspension was stirred magnetically for ten minutes, then titrated with the aid of a titration lamp using 0.05M ceric sulfate which was added from a 5 ml. microburette. The endpoint was taken at the complete decolorization of the liquid.

2. Injections and Solutions

An aliquot of the liquid preparation containing about 10 mg. of the active ingredient was accurately pipetted into a 10 ml. beaker. Five ml. of 2N sulfuric acid was added and the solution was titrated with the aid of a magnetic stirrer and a titration lamp using 0.05M ceric sulfate which was added from a 5 ml. microburette. The endpoint was taken at the complete decolorization of the solution. Some injections contained an anti-oxidant which was more easily oxidized than the phenothiazine drug itself and no color appeared upon the initial addition of titrant. Thus, readings were taken at the first appearance of color and at complete decolorization of the solution. The difference was the amount of titrant consumed by the drug.

3. Suppositories

Ten suppositories were weighed and reduced to fine particles. An amount of material approximately equivalent to 10 mg. of the active ingredient was accurately weighed into a 10 ml. beaker and dissolved in 3 ml. of chloroform. Three ml. of methanol was added and the solution was titrated with the aid of a magnetic stirrer and a titration lamp. The titrant was 0.05M ceric sulfate which was added from a 5 ml. microburette. The endpoint was taken at the complete decolorization of the solution.

RESULTS AND DISCUSSION

PURITY OF PHENOTHIAZINE DERIVATIVES INVESTIGATED

Table II lists the phenothiazine derivatives investigated, both bases and salts, together with their per cent purity as determined by the nonaqueous titration procedure outlined in the previous section. It was found that all the compounds had a purity of 98% or greater, with the exception of pipamazine base (97.85%) and pyrathiazine base (93.79%).

TITRATIONS WITH COPPER(II) IN ACETONITRILE

Although the use of nonaqueous solvents as media for acid - base reactions in analytical chemistry is now well established, little work has been done to investigate the use of these solvents in oxidation - reduction reactions. A large proportion of the work which has been reported in this area involved the utility of glacial acetic acid as solvent. Some interest has been focused on the use of acetonitrile as a solvent because it is highly resistant to oxidation or reduction. Also its moderately high dielectric constant promotes ionization of solutes and therefore more rapid electron transfer between species.

Kratochvil, Zatko and Markuszewski (30) recently found that copper(II) is a powerful oxidizing agent in acetonitrile; the formal reduction potential for the copper(II)-(I) couple is 0.798 v. vs. a Ag, 0.01M $AgNO_3$ reference electrode. This high value is caused by a

TABLE II. PURITY OF PHENOTHIAZINE DERIVATIVES INVESTIGATED.

Name of Drug	Per Cent Purity
Acetylpromazine Maleate	100.28
Aminopromazine Fumarate	98.37
Chlorpromazine Base	98.11
Chlorpromazine Hydrochloride	99.30
Fluphenazine Dihydrochloride	99.49
Levomepromazine Hydrochloride	98.82
Mepazine Acetate Hydrate	104.38
Methdilazine Base	99.11
Perphenazine Base	98.78
Pipamazine Base	97.85
Prochlorperazine Base	99.01
Prochlorperazine Dimaleate	98.42
Promazine Base	99.64
Promazine Hydrochloride	99.63
Promethazine Base	100.55
Pyrathiazine Base	93.79
Thiethylperazine Dimaleate	99.48
Thiopropazate Base	98.68
Thiopropazate Dihydrochloride	101.21
Thioridazine Base	98.79
Thioridazine Hydrochloride	99.84
Trifluoperazine Base	98.31
Trifluoperazine Dihydrochloride	100.02
Triflupromazine Hydrochloride	100.32
Trimeprazine Tartrate	99.30

large solvation energy for copper(I) in acetonitrile, which raises the potential of the copper(II)-(I) couple and lowers that of the copper(I)-(0) couple such that a difference of more than 1.5 v. exists between the two.

Billon (31), working with acetonitrile, showed that the potential of the first step in the oxidation of phenothiazine, that is the formation of the free radical, is 0.270 v. vs. a Ag, 0.01M Ag^+ reference electrode. He also found the potential of the second step, corresponding to the removal of an electron from the free radical to produce the phenazathionium ion, to be about 0.750 v., depending on the pH and the water content of the medium. Since the reduction potential for the copper(II)-(I) couple is 0.798 v., copper(II) should be a sufficiently strong oxidant to oxidize phenothiazine derivatives to the corresponding phenazathionium ion.

The titration of the free bases of several phenothiazine derivatives in acetonitrile with a standard solution of copper(II) perchlorate was attempted. The endpoint was detected both amperometrically (Table III) and photometrically (Table IV). Where the endpoint was determined amperometrically, a break in the curve corresponding to the addition of from 0.5 to 0.75 moles of copper per mole of phenothiazine was seen. The titration curves were quite rounded in the region of the endpoint, thus it was difficult to obtain reproducible

TABLE III. RESULTS OF AMPEROMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES IN ACETONITRILE WITH COPPER(II).

Name of Drug	$\frac{\text{moles Cu(II)}}{\text{moles drug}}$ at endpoint
Chlorpromazine Base	0.65
Levomepromazine Base	0.57
Perphenazine Base	0.75
Promethazine Base	0.63
Pyrathiazine Base	0.55
Thioridazine Base	0.50

TABLE IV. RESULTS OF PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES IN ACETONITRILE WITH COPPER(II).

Name of Drug	No Perchloric Acid Added		R* at endpoint with Perchloric Acid Added
	R* at 1st endpoint	R* at 2nd endpoint	
Chlorpromazine Base	1.23	2.82	1.49
Levomepromazine Base	0.85	2.54	1.49
Prochlorperazine Base	0.72	2.76	1.57
Promethazine Base	0.86	2.04	1.34
Thioridazine Base	0.92	2.64	1.58
Trifluoperazine Base	1.14	2.73	1.46
Methdilazine Base	1.16	2.65	1.47

* $R = \frac{\text{moles Cu(II)}}{\text{moles drug}}$

results by this method. A typical amperometric titration curve is shown in Figure 3. No color was produced in the solution during the titration until after the break in the amperometric curve.

The appearance of a color after the break in the amperometric titration curve suggested the use of a photometric technique for the determination of the end-point. Accordingly, the absorbance of the solution at the wavelength of maximum absorbance of the free radical formed by the particular phenothiazine derivative under investigation was plotted as a function of the amount of copper(II) perchlorate added.

As has been reported (25, 32), the nature of the substituent on the nitrogen of the phenothiazine nucleus has no effect on the wavelength of maximum absorption of the colored free radical intermediate produced upon partial oxidation of a phenothiazine derivative. However, phenothiazines with the same substituent in the 2-position all exhibit the same absorption maximum. The maximum occurs at 510 mμ in phenothiazines not substituted in the 2-position, at 500 mμ if the 2-substituent is a $-CF_3$ group, 525 mμ if -Cl, 575 mμ if $-OCH_3$, and at 645 mμ in thioridazine where the substituent is $-SCH_3$.

Results of titrations attempted with and without the addition of perchloric acid are listed in Table IV. If no acid was added to the solution, a graph with two

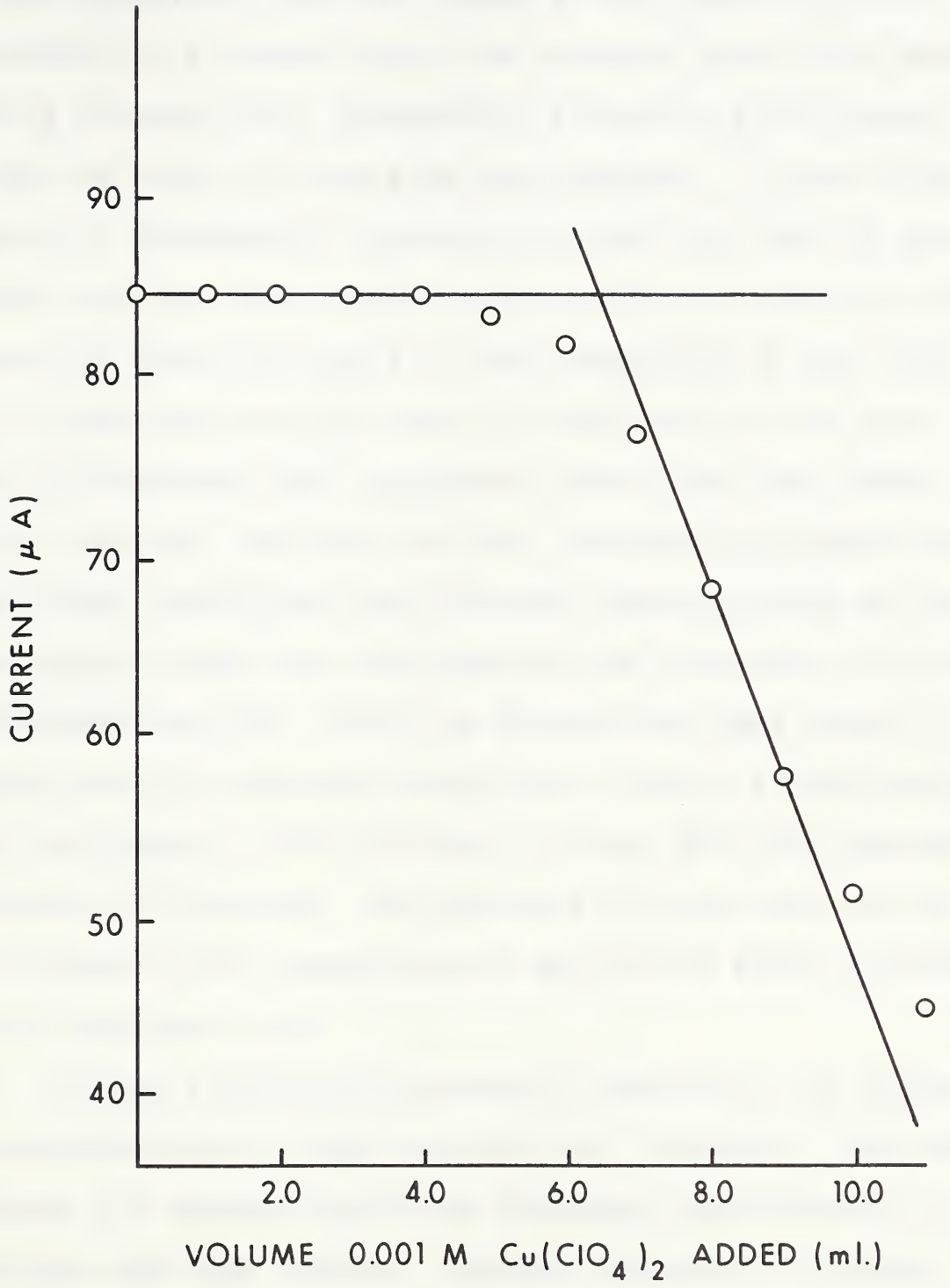


FIGURE 3 - TYPICAL AMPEROMETRIC TITRATION CURVE FOR TITRATION OF PHENOTHIAZINE DERIVATIVES WITH COPPER(II) PERCHLORATE

breaks, similar to the one shown in Figure 4a, resulted. If some perchloric acid was added to the solution prior to titration, a stable color was produced upon first addition of titrant and a photometric titration plot similar to the one shown in Figure 4b was obtained. In the first stage of a photometric titration carried out when no perchloric acid has been added to the solution, addition of copper(II) does not result in the production of any color. The colored free radical form is stabilized by the presence of hydrogen ions; apparently when none were added to the solution, the free radical intermediate cannot exist. Under these conditions, the oxidation does not stop at the free radical stage but continues to the formation of the phenazathionium ion. Since no precautions were taken to achieve totally anhydrous conditions, there is sufficient water available in the solution to react with the phenazathionium ion produced. The products of this reaction are the 5-oxide of the phenothiazine derivative being titrated and two hydrogen ions.

As the titration progresses, therefore, the hydrogen ion concentration of the solution will increase. When the hydrogen ion concentration has increased sufficiently to stabilize the free radical, further addition of titrant will result in the production of color and an apparent endpoint will be seen in the photometric titration curve. This apparent endpoint, as well as the endpoint obtained

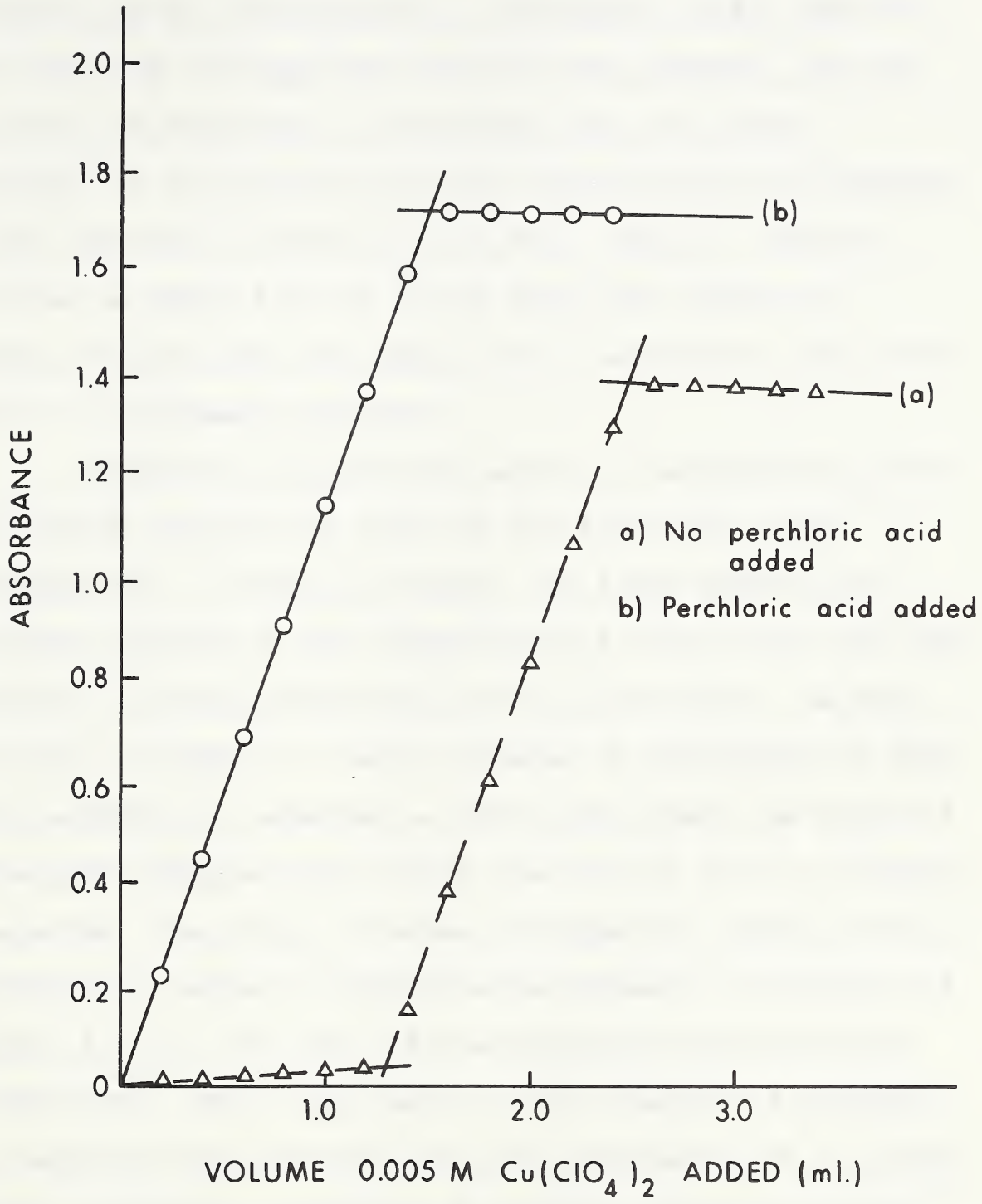


FIGURE 4 - TYPICAL PHOTOMETRIC TITRATION CURVES FOR TITRATION OF PHENOTHIAZINE DERIVATIVES WITH COPPER(II) PERCHLORATE

by amperometric titration where no perchloric acid was added, may not be expected to correspond to the addition of one mole of copper per mole of drug present, but may instead be dependent on variables such as initial acidity of the solution and the concentration of hydrogen ions required to stabilize the free radical. Results listed in Table III and in the first two columns of Table IV show that the molar ratio existing at this endpoint is extremely variable.

Addition of perchloric acid to the solution before titration changes the shape of the titration curve (Figure 4b). In this instance, the first addition of titrant results in the formation of a color since the free radical is being stabilized by the acid added. As more titrant is added, a linear increase in absorbance is seen. The endpoint is selected as that place where the slope of the graph changes from highly positive to zero or slightly negative. The ratio of moles of copper(II) added at the endpoint to moles of phenothiazine present in solution is about 1.5 to 1 for most of the phenothiazines titrated (Table IV). That this ratio is not integral is probably a result of more than one reaction proceeding at the same time. Initially, addition of titrant produces the free radical species which is stabilized by the presence of acid in the solution. If this were the only reaction proceeding, the photometric curve would increase to a maximum

after one equivalent of copper(II) had been added, and then decrease at the same rate as more titrant was added, since the additional titrant would oxidize the free radical to the colorless phenazathionium ion. However, it appears that these reactions occur simultaneously, so that by the time the absorbance due to the free radical species reaches a maximum, some of the free radical has reacted further.

If this hypothesis is correct, an increase in acid concentration would tend to decrease the rate of the second reaction relative to that of the first reaction because of the increased stability of the free radical which is formed by the first reaction. Thus the ratio of moles of copper(II) to moles of drug found at the endpoint should decrease to a limit of unity with increasing acid concentration. The effect of the concentration of perchloric acid on the molar ratio obtained in the titration of methdilazine base was investigated and the results do support the theory proposed. From a value of 1.47 at a perchloric acid concentration of 0.005N, which was the acid concentration used to obtain all the results listed in the last column of Table IV, the molar ratio decreased to a value of 1.42 at an acid concentration of 0.1N, 1.27 at an acid concentration of 1.0N and 1.18 when the acid concentration was increased to 2.0N. As the acid concentration was increased, the photometric titration curve

became more and more rounded in the region of the endpoint. If the acid concentration in the solvent was raised to more than 2N, this curvature made it impossible to determine an endpoint in the titration.

TITRATIONS WITH CERIC SULFATE

The use of cerium (IV) in aqueous solutions as a titrant for the analysis of phenothiazines has been extensively investigated by a number of Czechoslovakian workers (12-21). Since cerium (IV) is a very strong oxidizing agent (E° = 1.44 v. in 2N H_2SO_4), the phenothiazines are oxidized to the sulfoxide stage, thus the equivalence point in the titration corresponds to the addition of two moles of cerium (IV) to one mole of phenothiazine. The most convenient method of determining the endpoint in these titrations has been electrochemically, using the dead stop technique.

The titrations were carried out in aqueous solutions of sulfuric acid, thus the free radical intermediate was capable of prolonged existence. It was observed during the titrations that the color of the solution, due to the presence of the free radical species, increased to a maximum after one equivalent of titrant had been added, then the color decreased in intensity and disappeared entirely after two equivalents had been added. This latter situation corresponded to the dead stop endpoint. It appears

then, that a simple procedure could be devised in which this self-indicating property of phenothiazine derivatives might be utilized for their analysis. Accordingly, a series of titrations were carried out in which a pure phenothiazine derivative was dissolved in a dilute aqueous solution of sulfuric acid and titrated to a colorless endpoint with a standard solution of cerium (IV). Each derivative was titrated in several different concentrations of sulfuric acid. The results are summarized in Table V.

The recoveries obtained were invariably greater than 100 per cent. A correlation was seen between the extent of the error and the substituent in the 2-position of the phenothiazine nucleus. The best results were obtained when this substituent was a trifluoromethyl or acetyl group, while a gross overtitration resulted for thiethylperazine, which has a $-SCH_2CH_3$ group in the 2-position.

Kabasakalian and McGlotten (32) studied the effect of substituents in the 2-position on the polarographic half-wave potentials of various phenothiazine derivatives. The half-wave potential of a series of compounds with a common substituent in the 10-position increased as the 2-substituent was changed in the order -H, -Cl, $-COCH_3$, $-CF_3$. Thus the oxidation becomes more difficult as stronger electron withdrawing groups are attached to the ring. Although Kabasakalian and McGlotten did not report any results for compounds with ether or thioether substituents

TABLE V. RESULTS OF VISUAL TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE.

Name of Drug	$[H_2SO_4]$ in Solvent	Average Per Cent Recovered	Standard Deviation
Acetylpromazine Maleate	0.05	101.70	0.80
	0.2	105.64	4.47
	2	104.71	1.52
Chlorpromazine Base	0.5	105.36	0.99
	1	104.50	1.28
	2	104.09	0.93
	4	109.63	2.27
Fluphenazine Dihydrochloride	0.05	113.15	5.65
	1	116.35	4.92
	2	106.01	2.13
	4	109.24	4.76
Levomepromazine Hydrochloride	0.01	109.03	2.57
	0.025	112.69	2.17
	0.1	113.27	1.24
	1	113.81	2.03
	5	138.82	4.01
Mepazine Acetate Hydrate	0.05	109.57	1.61
	0.2	109.63	0.92
	2	111.25	2.88
Methdilazine Base	0.01	115.26	2.46
	0.05	115.90	1.84
	0.2	117.75	4.07
Perphenazine Base	0.2	138.19	10.31
	2	109.11	3.10
	4	114.90	4.50
Pipamazine Base	0.05	105.41	1.20
	0.2	104.40	1.28
	1	104.34	0.70
	2	104.73	1.35
Prochlorperazine Dimaleate	0.2	140.12	4.98
	1	112.59	2.33
	2	115.72	4.74
	4	116.09	1.30

...CONTINUED

TABLE V (CONTINUED) RESULTS OF VISUAL TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Average Per Cent Recovered	Standard Deviation
Promazine Hydrochloride	0.05	127.16	2.71
	0.2	127.35	5.72
	2	144.30	6.73
Pyrathiazine Base	0.05	109.77	5.56
	0.2	109.96	3.85
	2	114.23	3.91
Thiethylperazine Dimaleate	0.05	204.13	9.08
	0.2	163.05	8.04
	2	142.01	4.99
Thiopropazate Dihydrochloride	0.05	147.78	7.72
	0.2	144.24	9.21
	2	128.54	5.39
Thioridazine Base	0.05	118.42	4.40
	0.2	120.45	3.30
	2	120.73	9.22
Trifluperazine Dihydrochloride	0.05	129.59	15.69
	0.2	122.76	9.07
	2	106.23	1.16
	4	103.87	1.98
	6	106.48	1.89
Triflupromazine Hydrochloride	0.05	104.25	2.54
	0.2	101.93	1.56
	2	101.54	0.28
Trimeprazine Tartrate	0.05	111.12	3.05
	0.2	109.44	3.33
	2	107.95	9.42

in the 2-position, it is likely that the half-wave potentials of these compounds would be even lower than that of the corresponding compound which is unsubstituted in the 2-position, because of the electron donating property of these groups. Kabasakalian and McGlotten have shown that variations in the alkyl substituent in the 10-position of phenothiazine drugs have little effect on the oxidation potentials of these compounds. The position of the half-wave potential of phenothiazine derivatives will then vary with the nature of the 2-substituent in the order $-CF_3$, $-COCH_3$, -Cl, -H, $-OCH_3$, $-SCH_3$, $-SCH_2CH_3$, with a trifluoromethyl substituted compound being the most difficult to oxidize.

The recoveries obtained on titration with ceric sulfate vary in the same order as the ease of oxidation. The best results were obtained for derivatives which were the most difficult to oxidize, such as acetylpromazine and triflupromazine. It appears that cerium (IV) is such a strong oxidizing agent that the phenothiazine derivatives are being oxidized past the sulfoxide stage during the titration. When the endpoint, chosen by the disappearance of the color due to the free radical species, is reached, some of the titrant has already been consumed

in converting the sulfoxide to a higher oxidation state, probably the corresponding 3-hydroxyphenothiazine or 3-phenothiazone derivative. This competing reaction will probably proceed to a greater extent in compounds which are more easily oxidized. This is illustrated by thiethylperazine, the most easily oxidized member of the group, where the resulting error was greater than 50%. Compounds which are more resistant to oxidation, such as triflupromazine, can be determined by this method since oxidation of the free radical species to the sulfoxide stage may be complete before a significant amount of sulfoxide is converted to a higher oxidation state.

ANALYSIS OF PHARMACEUTICAL DOSAGE FORMS

The method of titration with ceric sulfate to a visual endpoint was also applied to certain pharmaceutical dosage forms of those phenothiazine derivatives for which the best results were obtained in the previous section. Results of these titrations are shown in Table VI.

Compressed tablets were analyzed simply by stirring

TABLE VI RESULTS OF VISUAL TITRATION OF PHENOTHIAZINE DOSAGE FORMS WITH CERIC SULFATE

Commercial Product	Labelled Contents	Per Cent Recovered	Standard Deviation
Chlorpromanyl ® "10" Tablets	Chlorpromazine HCl 11.2 mg./tablet	101.79	0.46
Largactil ® Tablets	Chlorpromazine HCl 55.8 mg./tablet	99.06	0.56
Largactil ® Spansule ® Capsules	Chlorpromazine HCl 30.0 mg./tablet	109.00	0.53
Largactil ® Suppositories	Chlorpromazine Base 25.0 mg./suppository	109.04	1.14
Chlorpromanyl ® Injection	Chlorpromazine HCl 27.9 mg./ml.	99.07	1.21
Largactil ® Injection	Chlorpromazine HCl 5.58 mg./ml.	96.67	1.28
Largactil ® Liquid	Chlorpromazine HCl 27.9 mg./5 ml.	127.64	0.28
Moditen ® Tablets	Fluphenazine HCl 1 mg./tablet	108.11	1.23
Stelazine ® Tablets	Trifluoperazine DiHCl 10 mg./tablet	101.64	0.82
Stelazine ® Injection	Trifluoperazine DiHCl 1 mg./ml.	110.44	2.99
Vesprin ® Injection	Triflupromazine HCl 20 mg./ml.	100.47	1.22

a quantity of the powdered tablet material magnetically with dilute sulfuric acid for several minutes, then titrating to the disappearance of color with ceric sulfate. Although insoluble tablet excipients remained suspended throughout the titration, no difficulty was seen in determining the point of decolorization of the liquid. Good results were obtained for chlorpromazine tablets and trifluoperazine tablets. The recovery obtained for fluphenazine tablets was high, but only slightly higher than the recovery obtained when the pure drug was analyzed by this method.

Chlorpromanyl® Injection and Largactil® Injection both contained a preservative which was more easily oxidized by ceric sulfate than was chlorpromazine. Thus initial addition of titrant did not result in the production of a red coloration, but a color did persist after all the preservative had been oxidized. From this point on the titration proceeded as before. The amount of chlorpromazine present was calculated on the basis of the amount of titrant added between the point at which the red color was first stable and the point at which decolorization occurred. Recoveries of less than 100% were found for both of the injections analyzed in this manner. In the analysis of trifluoperazine injection and trifluprom azine injection, an orange-brown color was produced upon first addition of titrant. Recoveries

obtained for both of these dosage forms were significantly higher than the results of the analysis of the pure drugs, perhaps because of the presence of an anti-oxidant in the injection which was titrated along with the phenothiazine. Attempts to analyze chlorpromazine liquid, suppositories and sustained-release capsules were not successful.

ULTRAVIOLET PHOTOMETRIC TITRATIONS WITH CERIC SULFATE

The ultraviolet absorption spectra of dilute sulfuric acid solutions of phenothiazine derivatives substituted with -H, -Cl, $-OCH_3$ or $-CF_3$ in the 2-position all show a strong peak at 250 to 255 mμ and a weaker, broad peak centered at about 300 mμ. Derivatives substituted with $-SCH_3$ or $-SCH_2CH_3$ in the 2-position also showed a weak, broad peak at 300 mμ, but the position of the stronger peak was shifted to 260 mμ. Chlorpromazine sulfoxide absorbs at 240 mμ, 273 mμ and 299 mμ. As would be expected, addition of two equivalents of ceric sulfate to a solution of chlorpromazine converted the chlorpromazine spectrum to that of chlorpromazine sulfoxide. Similarly, the addition of two equivalents of ceric sulfate to solutions of all phenothiazine derivatives with -H, -Cl, $-OCH_3$ or $-CF_3$ substituents in the 2-position resulted in spectra with strong absorption in the 240 mμ region and absorption peaks between 269 mμ and 273 mμ. The position of this latter peak was shifted to 275 mμ when the 2-substituent was a thioalkyl group.

Borg and Cotzias (33) found that the colored free radical produced by univalent oxidation of chlorpromazine gave rise to an ultraviolet spectrum different from that of either the drug itself or of its sulfoxide. The main peak of the free radical spectrum was centered at about 270 mμ, the same wavelength as the chlorpromazine sulfoxide peak. Due to the strong absorbance of the free radical species, addition of one equivalent of ceric sulfate to a solution of chlorpromazine resulted in a spectrum with stronger absorption at 270 mμ than the spectrum produced upon the addition of two equivalents of ceric sulfate. Similar results were seen for other phenothiazine derivatives with a chloro substituent in the 2-position and also for derivatives where this substituent was -H, $-CF_3$, or $-OCH_3$. The free radical produced by univalent oxidation of thioalkyl substituted phenothiazine derivatives, such as thioridazine and thiethylperazine, absorbs at a higher wavelength in the visible region than does the free radical of the other phenothiazine derivatives discussed. Thus this species would also be expected to absorb at a wavelength higher than 270 mμ in the ultraviolet region. Addition of one equivalent of ceric sulfate to a solution of thioridazine or thiethylperazine resulted in the production of a peak at 292 mμ.

Since the sulfoxide and the free radical species derived from thioalkyl substituted phenothiazines absorb

at different wavelengths in the ultraviolet region, the absorption due to the sulfoxide species produced during the titration can be measured without interference from the free radical intermediate. Photometric titrations of these compounds at a wavelength of 275 mμ resulted in a curve such as that shown in Figure 5b. The absorbance increased linearly with the addition of ceric sulfate until two equivalents of titrant had been added and then remained constant with the addition of further increments of titrant. Recoveries of thiethylperazine and thioridazine obtained by this method were 98.36% and 98.10% respectively.

Photometric titrations with ceric sulfate were also attempted for phenothiazine derivatives without thioalkyl substituents. With these compounds, the absorption of the free radical interfered with that of the sulfoxide at 270 mμ. Thus a peak was produced in the photometric titration curve after the addition of one equivalent of titrant, corresponding to the maximum intensity of the free radical absorption. The absorption at 270 mμ decreased with the addition of the second equivalent of titrant as the free radical was being converted to the sulfoxide. After two equivalents of ceric sulfate had been added, the absorbance, now due only to the sulfoxide, remained constant with the addition of further increments

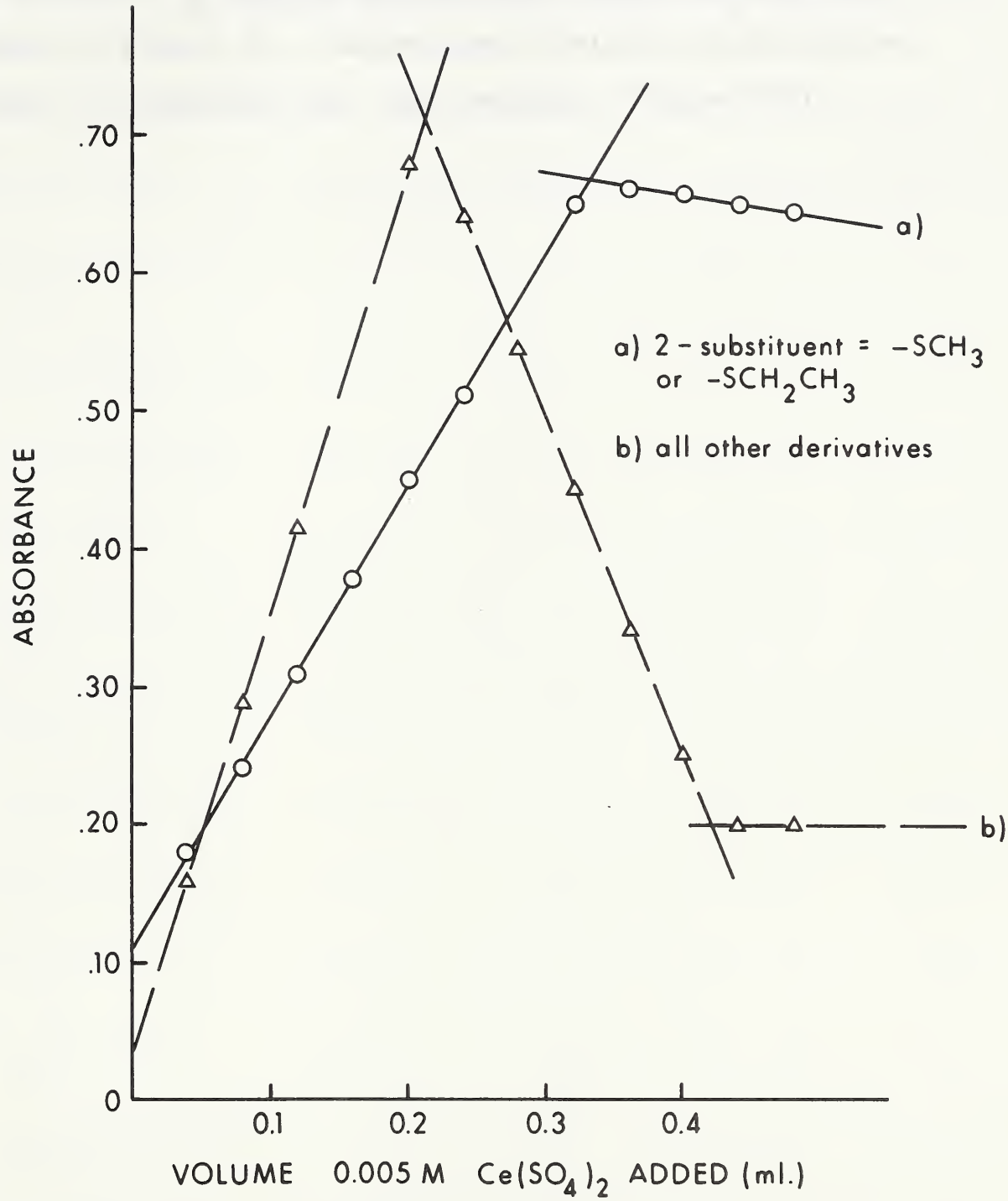


FIGURE 5 - TYPICAL ULTRAVIOLET PHOTOMETRIC TITRATION CURVES FOR TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

of titrant. A typical photometric titration curve is shown in Figure 5a. Recoveries obtained for the latter class of compounds were very variable (Table VII).

TABLE VII RESULTS OF ULTRAVIOLET PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	1:1 Break		2:1 Break	
	% Recovered	Standard Deviation	% Recovered	Standard Deviation
Chlorpromazine Base	113.65	4.77	110.14	2.98
Fluphenazine Dihydrochloride	115.45	0.58	117.56	2.15
Levomepromazine Hydrochloride	122.36	4.18	107.06	2.51
Methdilazine Base	108.48	2.54	108.59	2.49
Perphenazine Base	108.79	3.59	108.10	3.10
Pipamazine Base	113.41	2.04	115.17	7.06
Prochlorperazine Dimaleate	110.64	3.54	111.23	2.90
Promazine Hydrochloride	83.84	2.55	84.53	2.95
Promethazine Base	110.84	3.65	117.31	2.86
Pyrathiazine Base	105.29	3.38	106.62	2.18
Thiethylperazine Dimaleate	-	-	98.36	2.05
Thiopropazate Dihydrochloride	100.08	1.86	105.03	3.77
Thioridazine Base	-	-	98.10	1.00
Trifluoperazine Dihydrochloride	114.36	1.93	125.59	1.10
Triflupromazine Hydrochloride	94.48	1.80	116.34	0.81
Trimeprazine Tartrate	89.84	0.99	94.08	1.18

SUMMARY AND CONCLUSIONS

(1) Attempts to develop quantitative procedures for phenothiazine derivatives by titration with copper(II) in acetonitrile were unsuccessful. A possible explanation of the unfavorable results obtained is postulated.

(2) A method was developed in which phenothiazine derivatives were titrated to a colorless endpoint in dilute sulfuric acid solution. The titrant was ceric sulfate. Quantitative recoveries were obtained only for chlorpromazine, acetylpromazine, trifluoperazine and triflupromazine. The method was applied to available pharmaceutical dosage forms of these drugs. A possible explanation is advanced for the unfavorable results obtained for other phenothiazines investigated.

(3) A method was developed in which the endpoint in the titration of phenothiazine derivatives with ceric sulfate was detected photometrically by following the absorbance of the sulfoxide in the ultraviolet region. This method was found to be applicable only to phenothiazine derivatives which were substituted with a thioalkyl group in the 2-position. A reason for the failure of this technique for other phenothiazine derivatives is advanced.

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APPENDIX

TABLE VIII. DATA FOR ANALYSIS OF PHENOTHIAZINE DERIVATIVES BY NONAQUEOUS TITRATION.

Name of Drug	Sample Weight (mg.)	Titrant Volume (ml.)	Per Cent Recovered	Average Per Cent Recovered
Acetylpromazine Maleate	34.40	0.785	100.48	
	37.25	0.845	99.88	100.28
	37.25	0.859	100.47	
Aminopromazine Fumarate	20.30	1.055	99.20	
	19.70	1.010	97.84	98.37
	22.20	1.140	98.06	
Chlorpromazine Base	33.10	1.025	98.24	
	32.55	1.005	87.98	98.11
	31.85	0.985	98.12	
Chlorpromazine Hydrochloride	35.45	0.995	99.24	
	39.95	1.125	99.53	99.30
	35.85	1.005	99.12	
Fluphenazine Dihydrochloride	25.40	1.000	99.99	
	32.00	1.245	98.81	99.49
	26.50	1.040	99.67	
Levomepromazine Base	39.80	1.200	98.52	
	32.30	0.980	99.11	98.82
	36.90	1.115	98.75	
Levomepromazine Hydrochloride	36.50	0.995	98.93	
	40.80	1.115	99.15	98.94
	36.95	1.005	98.75	
Mepazine Acetate Hydrate	36.50	0.985	104.33	
	35.80	0.955	103.13	104.38
	36.40	0.995	105.68	
Methdilazine Base	30.30	1.020	99.37	
	26.55	0.890	98.96	99.11
	28.30	0.950	99.00	
Perphenazine Base	40.20	0.985	98.48	
	39.35	0.970	99.11	98.78
	38.05	0.935	98.75	
Pipamazine Base	36.40	0.890	97.80	
	41.70	1.020	97.89	97.85
	45.60	1.115	97.85	

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TABLE VIII (CONTINUED) DATA FOR ANALYSIS OF PHENOTHIAZINE DERIVATIVES BY NONAQUEOUS TITRATION

Name of Drug	Sample Weight (mg.)	Titrant Volume (ml.)	Per Cent Recovered	Average Per Cent Recovered
Prochlorperazine Base	35.95	0.955	98.85	
	40.30	1.075	99.24	99.01
	41.55	1.105	98.93	
Prochlorperazine Dimaleate	32.15	1.060	99.41	
	32.75	1.055	97.13	98.42
	33.90	1.110	98.73	
Promazine Base	31.95	1.125	99.67	
	28.25	0.995	99.66	99.64
	28.55	1.005	99.60	
Promazine Hydrochloride	32.10	1.000	99.55	
	36.05	1.125	99.63	99.63
	31.85	0.995	99.72	
Promethazine Base	32.85	1.165	100.40	
	35.60	1.265	100.60	100.55
	31.25	1.110	100.65	
Pyrathiazine Base	31.00	0.985	93.78	
	34.75	1.105	93.76	93.79
	34.10	1.085	93.84	
Thiethylperazine Dimaleate	24.25	0.765	99.15	
	29.70	0.945	100.00	99.48
	36.25	1.145	99.28	
Thiopropazate Base	45.85	1.015	98.23	
	51.75	1.155	99.05	98.68
	44.70	0.995	98.75	
Thiopropazate Dihydrochloride	23.00	0.905	101.02	
	26.40	1.035	101.22	101.21
	23.55	0.925	101.40	
Thioridazine Base	36.00	0.965	98.84	
	42.35	1.125	97.96	98.79
	37.20	1.005	99.58	
Thioridazine Hydrochloride	41.00	1.110	99.81	
	39.75	1.075	99.67	99.84
	38.51	1.045	100.05	

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TABLE VIII (CONTINUED) DATA FOR ANALYSIS OF PHENOTHIAZINE DERIVATIVES BY NONAQUEOUS TITRATION

Name of Drug	Sample Weight (mg.)	Titrant Volume (ml.)	Per Cent Recovered	Average Per Cent Recovered
Trifluperazine Base	41.90	1.015	98.18	
	40.55	0.985	98.45	98.31
	39.60	0.960	98.30	
Trifluperazine Dihydrochloride	23.55	0.985	99.97	
	24.15	1.015	100.46	100.02
	24.95	1.040	99.63	
Triflupromazine Base	36.65	0.945	99.77	
	39.45	1.025	100.54	100.32
	35.75	0.930	100.66	
Trimeprazine Tartrate	37.65	1.000	98.70	
	41.60	1.120	100.05	99.30
	40.10	1.070	99.16	

TABLE IX. DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Acetylpromazine Maleate	0.05	9.95	104.65	
		10.90	103.41	
		9.00	99.94	
		10.25	107.80	105.64
		10.80	112.59	
		10.00	111.05	
		10.50	104.18	
		10.45	101.49	
	0.2	10.20	100.71	
		10.80	101.28	
		10.50	101.53	101.70
		10.70	102.75	
		10.70	102.23	
	2	11.50	102.84	
		10.40	106.26	
		12.80	104.11	104.71
		10.00	103.83	
		11.30	106.14	
		10.25	105.09	
Chlorpromazine Base	0.5	10.20	105.52	
		11.20	106.46	105.36
		9.95	103.75	
		9.35	105.70	
	1	9.05	103.46	
		6.90	103.80	
		9.95	104.15	104.50
		10.35	106.70	
		7.55	104.40	
	2	7.60	103.72	
		8.20	104.91	
		9.10	104.65	
		8.60	102.35	
		8.30	103.16	104.09
		6.65	104.69	
		7.05	104.43	
		7.10	104.82	

...CONTINUED

TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Chlorpromazine Base (continued)	4	7.20	110.03	
		7.55	110.23	
		7.05	108.96	109.63
		7.30	106.33	
		8.60	112.59	
Fluphenazine Dihydrochloride	0.05	12.65	106.83	
		11.30	111.10	
		10.05	113.33	113.15
		10.40	121.33	
	1	10.164	117.85	
		10.164	112.17	
		10.164	127.30	
		10.164	119.74	116.35
		10.164	115.32	
		10.164	114.69	
		10.164	112.80	
		10.164	112.80	
		10.164	110.91	
	2	7.25	106.90	
		10.45	102.36	
		8.35	106.63	106.01
		6.45	106.26	
		7.30	107.92	
	4	10.228	112.72	
		10.228	104.58	
		10.228	119.61	
		10.228	104.58	
		10.228	105.21	109.24
		10.224	114.02	
		10.224	109.64	
		10.224	107.13	
		10.224	107.00	
		10.224	110.89	
Levomepromazine Hydrochloride	0.01	7.35	105.42	
		6.85	110.71	
		9.85	112.12	109.03
		7.40	108.05	
		7.80	108.85	

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TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Levomepromazine Hydrochloride (continued)	0.025	8.516	115.60	
		8.516	113.45	
		8.516	112.38	
		8.516	113.99	
		8.516	113.45	112.69
		8.176	112.01	
		8.176	110.89	
		8.176	109.78	
	0.1	8.516	111.84	
		8.516	113.99	113.27
		8.516	113.99	
	1	8.516	116.14	
		8.516	112.38	113.81
		8.516	112.91	
	5	8.516	139.80	
		8.176	142.25	138.82
		8.176	134.82	
Mepazine Acetate Hydrate	0.05	9.45	111.95	
		7.90	108.61	
		10.85	110.53	109.57
		9.40	108.40	
		10.35	108.34	
	0.2	8.90	109.56	
		7.00	109.34	
		10.00	108.72	109.63
		8.00	110.91	
		8.20	-	
	2	8.85	107.97	
		7.85	110.55	
		8.95	115.48	111.25
		9.60	109.69	
		7.45	112.56	

...CONTINUED

TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	[H_2SO_4] in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Methdilazine Base	0.01	9.05	115.90	
		7.00	117.43	
		10.00	116.05	115.26
		8.15	115.92	
		6.60	111.02	
	0.05	11.05	115.46	
		9.00	119.03	
		8.65	114.90	115.90
		8.35	115.82	
		6.90	114.28	
	0.2	6.10	113.42	
		10.70	115.76	
		13.30	-	117.75
		9.50	119.03	
		8.30	122.79	
Perphenazine Base	0.2	8.10	133.92	
		11.50	148.55	
		10.20	133.19	138.19
		7.85	125.92	
		9.30	149.35	
	2	7.95	104.57	
		7.65	108.01	
		6.25	110.30	109.11
		11.35	112.99	
		9.15	109.69	
	4	8.30	119.70	
		6.05	118.14	
		8.20	108.18	114.90
		9.30	113.37	
		7.75	115.11	
Pipamazine Base	0.05	10.90	106.43	
		13.30	105.04	
		10.40	104.27	105.41
		11.50	104.38	
		10.00	106.92	

...CONTINUED

TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Pipamazine Base (continued)	0.2	9.70	103.99	
		12.00	104.24	
		12.35	105.37	104.40
		8.95	102.57	
		11.20	105.83	
	1	10.95	104.10	
		13.80	100.87	
		11.40	103.53	104.34
		10.50	105.20	
		11.00	104.54	
	2	8.10	105.23	
		8.15	106.44	
		10.30	102.83	104.73
		10.95	104.10	
		7.25	105.05	
Prochlorperazine Dimaleate	0.2	10.30	132.16	
		11.40	142.09	
		10.35	144.01	140.12
		12.30	138.49	
		11.10	143.87	
	1	10.638	112.95	
		10.638	110.09	
		10.638	114.38	112.59
		10.638	109.37	
		10.638	113.66	
		10.638	115.09	
	2	9.00	119.91	
	Base	10.90	112.78	115.72
		14.70	112.35	
		13.10	121.77	
		8.10	111.78	
	4	10.638	114.38	
		10.638	117.24	
		10.638	115.09	116.09
		10.638	116.52	
		10.638	117.24	

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TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Promazine Hydrochloride	0.2	8.60	128.28	
		6.30	125.26	
		7.25	130.51	127.16
		7.70	123.40	
		8.25	128.35	
	0.05	6.75	125.26	
		9.55	131.96	
		8.55	134.20	127.35
		7.55	119.99	
		8.00	125.32	
	2	6.95	139.04	
		8.80	150.98	
		8.05	149.04	144.30
		9.75	147.01	
		8.80	135.43	
Pyrathiazine Base	.05	6.65	102.36	
		8.20	106.59	
		8.10	110.20	109.77
		8.30	117.40	
		7.45	109.33	
	0.2	7.90	103.58	
		8.95	113.87	
		7.50	111.08	109.96
		7.85	111.34	
		8.90	109.91	
	2	8.50	114.64	
		8.90	107.82	
		9.50	115.10	114.23
		9.10	118.53	
		8.60	115.04	
Thiethylperazine Dimaleate	0.05	7.95	187.46	
		8.30	209.16	
		9.65	209.47	204.13
		11.00	210.43	
		8.60	-	

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TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Thiethylperazine Dimaleate (continued)	0.2	9.70	156.09	
		8.10	150.71	
		9.35	174.65	163.05
		8.00	163.49	
		8.75	170.32	
	2	11.65	131.32	
		8.65	146.63	
		8.05	144.75	142.01
		7.85	144.40	
		9.65	142.93	
Thiopropazate Dihydrochloride	0.05	9.05	142.46	
		11.70	141.92	
		10.65	143.07	147.78
		8.70	159.42	
		10.75	152.03	
	0.2	9.05	142.46	
		9.45	136.43	
		9.65	140.35	144.24
		8.45	141.79	
		9.35	160.17	
	2 (Base)	7.95	122.48	
		16.40	127.96	
		14.15	137.24	128.54
		10.60	126.71	
		11.95	128.31	
Thioridazine Base	0.05	5.85	114.45	
		8.80	119.41	
		10.55	124.28	118.42
		8.00	120.31	
		7.65	113.66	
	0.2	7.30	116.56	
		8.20	122.47	
		10.70	117.76	120.45
		7.80	124.58	
		9.00	120.88	

...CONTINUED

TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Thioridazine Base (continued)	2	7.75	118.19	
		8.65	118.25	120.73
		6.90	112.53	
		5.90	133.97	
Trifluoperazine Dihydrochloride	0.05	8.75	125.39	
		6.75	116.10	
		9.40	155.19	129.59
		11.00	132.62	
		9.35	118.63	
	0.2	9.20	117.29	
		9.15	118.58	
		7.65	126.87	122.76
		8.60	136.69	
		8.75	114.76	
	2	8.75	105.18	
		9.80	107.48	
		10.10	106.31	106.23
		10.25	107.25	
		7.60	104.95	
	4	8.85	101.10	
		7.45	106.38	103.87
		8.05	102.89	
		9.05	104.52	
		9.25	104.47	
	6	9.70	104.90	
		8.70	105.79	
		11.20	109.11	106.48
		12.05	107.78	
		10.00	104.82	
Trifluprom azine Hydrochloride	0.05	8.05	101.84	
		7.60	106.58	
		8.45	107.41	104.25
		10.10	103.88	
		11.20	101.52	

...CONTINUED

TABLE IX (CONTINUED) DATA FOR VISUAL TITRATIONS OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	$[H_2SO_4]$ in Solvent	Sample Weight (mg.)	Per Cent Recovered	Average Per Cent Recovered
Trifluprom azine Hydrochloride (continued)	0.2	10.10	100.01	
		7.80	103.22	
		10.30	101.86	101.93
		8.75	103.73	
		7.50	100.85	
	2	8.20	101.16	
		8.10	101.81	101.54
		10.30	101.86	
		9.50	101.19	
		9.60	101.66	
Trimeprazine Tartrate	0.05	11.10	111.46	
		11.20	111.72	
		11.90	109.08	111.12
		7.95	108.46	
		11.30	114.82	
	0.2	10.35	113.65	
		8.75	110.33	
		9.80	108.55	109.44
		7.90	106.18	
		9.85	108.48	
	2	8.10	105.30	
		9.70	113.54	
		10.45	113.46	107.95
		8.90	95.31	
		8.40	112.14	

TABLE X DATA FOR VISUAL TITRATION OF PHENOTHIAZINE DOSAGE FORMS WITH CERIC SULFATE

Commercial Product	Average Weight per Unit of Solid (gm.)	Amount Taken (gm. or ml.)	Per Cent Recovered	Average Per Cent Recovered
Chlorpromanyl® "10" Tablets	0.13512	0.13510	102.43	101.79
		0.13510	101.63	
		0.13510	102.03	
		0.13510	101.63	
		0.13510	101.23	
Largactil® Tablets	0.20248	0.03780	99.45	99.06
		0.04310	98.50	
		0.03900	98.88	
		0.04320	98.64	
		0.04155	99.83	
Largactil® Spansule® Capsules	0.17478	0.04990	108.80	109.00
		0.05050	109.57	
		0.04585	108.21	
		0.04610	109.32	
		0.05260	109.14	
Largactil® Suppositories	1.11612	0.37330	110.06	109.04
		0.38255	107.40	
		0.35380	110.07	
		0.35810	109.24	
		0.35915	108.43	

...(CONTINUED)

TABLE X (CONTINUED) DATA FOR VISUAL TITRATION OF PHENOTHIAZINE DOSAGE FORMS WITH CERIC SULFATE

Commercial Product	Average Weight per Unit of Solid (gm.)	Amount Taken (gm. or ml.)	Per Cent Recovered	Average Per Cent Recovered
Chlorpromanyl ® Injection		0.80	97.43	
		0.80	100.63	
		0.80	99.63	99.07
		0.80	98.43	
		0.80	99.23	
Largactil ® Injection		2.00	98.43	
		2.00	96.83	
		2.00	96.83	99.67
		2.00	94.83	
		2.00	96.43	
Largactil ® Liquid		2.00	128.04	
		2.00	127.64	
		2.00	127.24	127.64
		2.00	127.64	
		2.00	127.64	
Moditen ® Tablets		0.49300	107.50	
		0.48590	106.70	
	0.17988	0.48970	108.23	108.11
		0.50265	110.02	
		0.51150	108.12	

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TABLE X (CONTINUED) DATA FOR VISUAL TITRATION OF PHENOTHIAZINE DOSAGE FORMS WITH CERIC SULFATE

Commercial Product	Average Weight per Unit of Solid (gm.)	Amount Taken (gm. or ml.)	Per Cent Recovered	Average Per Cent Recovered
Stelazine® Tablets		0.46350	101.32	
		0.46260	102.56	
	0.46862	0.48240	102.32	101.64
		0.49585	100.51	
		0.47680	101.51	
Stelazine® Injection		1.00	107.37	
		1.00	112.49	
		1.00	112.49	110.44
		1.00	112.49	
		1.00	107.37	
Vesprin® Injection		1.00	99.06	
		1.00	101.25	
		1.00	101.01	100.47
		1.00	101.01	
		1.00	99.06	
		1.00	100.03	

TABLE XI DATA FOR ULTRAVIOLET PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	Sample Weight (mg.)	1:1 Break Per Cent Recovered	1:1 Break Average Per Cent Recovered	2:1 Break Per Cent Recovered	2:1 Break Average Per Cent Recovered
Chlorpromazine Base	0.2230	107.65		111.96	
	0.2230	120.57		111.96	
	0.2165	111.96	113.65	107.65	110.14
	0.2250	115.43		106.25	
	0.2200	112.65		112.90	
Fluphenazine Dihydrochloride	0.4205	115.16		115.78	
	0.4205	115.78		120.95	
	0.4205	115.16	115.45	115.78	117.56
	0.4115	116.25		118.23	
	0.4170	114.78		117.05	
Levomepromazine Hydrochloride	0.223	127.30		104.72	
	0.223	117.45		110.47	
	0.2180	119.09	122.36	104.72	107.06
	0.2250	122.35		108.63	
	0.2215	125.62		106.75	
Methdilazine Base	0.2390	105.21		105.82	
	0.2390	108.94		108.01	
	0.2390	111.43	108.48	112.05	108.59
	0.2415	110.15		110.10	
	0.2350	106.65		107.20	

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TABLE XI (CONTINUED) DATA FOR ULTRAVIOLET PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	Sample Weight (mg.)	1:1 Break Per Cent Recovered	1:1 Break Average Per Cent Recovered	2:1 Break Per Cent Recovered	2:1 Break Average Per Cent Recovered
Perphenazine Base	0.2715	105.30		104.56	
	0.2715	106.05		107.54	
	0.2685	114.26	108.79	112.02	108.10
	0.2700	110.12		110.17	
	0.2735	108.23		106.23	
Pipamazine Base	0.3140	115.01		115.01	
	0.3140	115.65		106.98	
	0.3000	110.51	113.41	124.97	115.17
	0.3250	112.65		110.25	
	0.3185	113.25		118.65	
Prochlorperazine Dimaleate	0.3715	114.63		114.63	
	0.3715	106.44		109.72	
	0.3650	113.81	110.64	113.81	111.23
	0.3725	110.24		110.24	
	0.2705	108.12		107.75	
Promazine Hydrochloride	0.2400	81.87		82.87	
	0.2400	81.87		87.24	
	0.2415	86.56	83.84	83.88	84.53
	0.2465	82.20		80.84	
	0.2440	86.69		87.81	

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TABLE XI (CONTINUED) DATA FOR ULTRAVIOLET PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	Sample Weight (mg.)	1:1 Break Per Cent Recovered	1:1 Break Average Per Cent Recovered	2:1 Break Per Cent Recovered	2:1 Break Average Per Cent Recovered
Promethazine Base	0.2020	109.53		117.31	
	0.2020	105.29		116.25	
	0.2115	111.65	110.84	118.01	117.31
	0.1985	112.88		121.42	
	0.2075	114.85		113.54	
Pyrathiazine Base	0.2500	107.12		109.79	
	0.2500	101.76		106.52	
	0.2485	104.14	105.29	105.03	106.62
	0.2465	110.20		104.25	
	0.2515	103.21		107.50	
Thiethylperazine Dimaleate	0.3910			97.72	
	0.3910			101.37	
	0.3925			99.75	
	0.3865			86.20	98.36
	0.3915			96.20	
	0.3920			98.90	
Thiopropazate Dihydrochloride	0.3880	101.36		108.80	
	0.3880	99.35		99.35	
	0.3685	97.65	100.08	108.08	105.33
	0.3750	102.43		104.32	
	0.3900	99.60		106.12	

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TABLE XI (CONTINUED) DATA FOR ULTRAVIOLET PHOTOMETRIC TITRATION OF PHENOTHIAZINE DERIVATIVES WITH CERIC SULFATE

Name of Drug	Sample Weight (mg.)	1:1 Break Per Cent Recovered	1:1 Break Average Per Cent Recovered	2:1 Break Per Cent Recovered	2:1 Break Average Per Cent Recovered
Thioridazine Base	0.2400			98.42	
	0.2400			97.25	
	0.2385			96.87	98.10
	0.2425			99.23	
	0.2410			98.75	
Trifluoperazine Dihydrochloride	0.3175	116.96		125.31	
	0.3175	113.92		126.07	
	0.3240	111.64	114.36	126.45	125.59
	0.3160	114.23		123.78	
	0.3200	115.05		126.32	
Trifluprom azine Hydrochloride	0.2505	91.95		116.49	
	0.2505	96.62		116.49	
	0.2565	93.50	94.48	116.49	116.34
	0.2475	95.45		115.02	
	0.2515	94.86		112.23	
Trimeprazine Tartrate	0.2490	88.84		95.23	
	0.2490	89.59		92.22	
	0.2500	91.09	89.84	94.85	94.04
	0.2525	89.04		93.65	
	0.2485	90.65		94.25	